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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/521,691	08/31/2005	Masayasu Okochi	10873.1604USWO	4565

52835 7590 04/27/2009

HAMRE, SCHUMANN, MUELLER & LARSON, P.C.
P.O. BOX 2902
MINNEAPOLIS, MN 55402-0902

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	
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04/27/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/521,691	OKOCHI ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 6-21* is/are pending in the application.

4a) Of the above claim(s) *12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-11 and 20* is/are rejected.

7)☒ Claim(s) *6 and 19* is/are objected to.

8)☒ Claim(s) *1-3, 6-21* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2008 and 18 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Revised Notice to Comply; PTO-90C; Defective Sequence Compliance Attachment*.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendments of 05 February 2009 and 20 October 2008 have been entered in full. Claims 1, 6, 7, 13, 15, 17 are amended. Claims 4-5 are cancelled. Claims 19-21 are added.

Election/Restrictions

Applicant's election with traverse of Group 13 in the reply filed on 05 February 2009 is acknowledged. The traversal is on the ground(s) that the present claims have unity of invention at least in view of the special technical feature of the S4 cleavage site, which was not recognized in the literature prior to the present application. Applicant indicates that if this argument is not accepted, at least the sequences 10-18, which represent human amino acid sequences, could be examined together without undue burden. This is not found persuasive *in part*. Specifically, amended claim 1 is still anticipated by the prior art (Mumm et al.; see 102 rejections below). Claim 1 lacks a special technical feature and cannot share one with the other claims. However, after reviewing the amino acid sequences of SEQ ID NOs: 10-18 and observing their similarity, the Examiner is *withdrawing* the restriction requirement among Groups 10-18 as set forth in the previous Office Action of 07 January 2009. The amino acid sequences of SEQ ID NO:s 10-18 are hereby rejoined.

The requirement is still deemed proper and is therefore made FINAL.

Claims 12-18 and 21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 05 February 2009 and 26 March 2008.

Claims 1-3, 6-11, 19-20 are under consideration in the instant application as they read upon elected SEQ ID NOs: 10-18.

Priority

Receipt is acknowledged of the translation of foreign priority paper, JAPAN 2002-210040, on 18 June 2008.

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (20 October 2008) has been considered. However, the CRF could not be accepted by the STIC Systems Branch. Specifically, the response for numeric identifier <223> is insufficient. When using "artificial" for numeric identifier <213>, please provide as much taxonomic information as possible about the organism from which the genetic material was extracted. This application fails to comply with the requirements of 37 CFR 1.821 through 1.825. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825). Please see the attached Revised Notice to Comply, PTO-90C, and STIC Systems Branch Annotations Sheet.

Withdrawn Objections and/or Rejections

1. The objections to claims 1, 4, 5 at page 3 of the previous Office Action (18 June 2008) are *withdrawn* in view of the amended and cancelled claims (20 October 2008).

2. The rejection of claims 1-5 under 35 U.S.C. § 101 (product of nature) as set forth at pages 3-4 of the previous Office Action (18 June 2008) is *withdrawn* in view of the amended claims (20 October 2008).

3. The rejections of claims 1-5 under 35 U.S.C. § 112, second paragraph, as set forth at pages 4-6 of the previous Office Action (18 June 2008) are *withdrawn* in view of the amended claims and cancelled claims (20 October 2008). Please see section on 35 U.S.C. 112, second paragraph below.

4. The rejection of claims 1-5 under 35 U.S.C. § 102(a) as being anticipated by Okochi et el. is *withdrawn* in view of the translation of the foreign priority papers filed on 18 June 2008.

Claim Objections

5. Claims 1, 6, 7, 19, 20 are objected to because of the following informalities:

5a. In claim 1, line 4, the phrase "near a surface of cell membrane" should be amended to recite, for example, "near the surface of a cell membrane".

5b. In claim 7, line 6, the phrase "near a surface of cell membrane" should be amended to recite, for example, "near the surface of a cell membrane".

5c. Claims 6, 7, 19, 20 recite non-elected inventions.

5d. In claims 6, 7, 19, 20, the term "SEQ ID NOS" should be amended to recite "SEQ ID NOs".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-3, 7-11, 19-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 1-3, 7-11, and 19-20 are rejected as being indefinite because the claims are directed to an isolated or synthesized polypeptide. However, claims 1 and 7 also recite, for example, "Site-2 cleavage site of the Notch protein that is positioned near a surface of cell membrane" and "Site-3 cleavage site is positioned at either inside the cell membrane or in close proximity to the cell membrane inside the cell". Thus, it seems as if the claimed polypeptide has not been isolated.

8. Claims 1-3, 7-11, and 19-20 are rejected as being indefinite because claims 1 and 7 recite "Site-4 cleavage site of the Notch protein that is positioned on N-terminal side in a transmembrane domain of the Notch protein" (see claim 1, lines 5-6 and claim 7, lines 7-8). Claims 1 and 7 later recite that the polypeptide comprises at least a part of the transmembrane domain of the Notch protein (see claim 1, lines 9-10 and claim 7, lines 11-12). It is not clear if the claimed polypeptide comprises an entire Notch protein transmembrane domain or a part of a Notch protein transmembrane domain.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-3, 7-11, 20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated or synthesized polypeptide wherein the

polypeptide consists of (i) a Notch extracellular truncation (NEXT) fragment from a Notch protein, (ii) a Site-2 cleavage site of the Notch protein positioned at the N-terminus of the NEXT fragment, and (iii) a Site-4 cleavage site of the Notch protein positioned at the C-terminus of the NEXT fragment, **does not reasonably provide enablement for** an isolated or synthesized polypeptide wherein the polypeptide is a fragment of a Notch protein, a Site-2 cleavage site at the N-terminal of the polypeptide. Furthermore, the specification, while being enabling for a biomarker of Notch signal transduction, does not reasonably provide enablement for a biomarker of cell differentiation, tumor, apoptosis, or Alzheimer's disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to an isolated or synthesized polypeptide, wherein the polypeptide is a fragment of a Notch protein, N-terminal of the polypeptide is Site-2 cleavage site of the Notch protein that is positioned near a surface of cell membrane, C-terminal of the polypeptide is Site-4 cleavage site of the Notch protein that is positioned on N-terminal side in a transmembrane domain of the Notch protein relative to Site-3 cleavage site, wherein the Site-3 cleavage site is positioned at either inside the cell membrane or in close proximity to the cell membrane inside the cell, the polypeptide comprises at least a part of the transmembrane domain of the Notch protein, the polypeptide is produced and released to an extracellular space as a result of proteolysis at the Site-4 cleavage site that occurs simultaneously with, before, or after proteolysis at the Site-3 cleavage site, wherein the proteolysis at the Site-3 cleavage site occurs subsequent to proteolysis at the Site-2 cleavage site and translocates Notch intracellular cytoplasmic domain (NICD) to a nucleus of the cell, and the Notch protein is a Notch protein that exists in an at least

one organism selected from the group consisting of a human, a mouse, a rat, a rabbit, a goat, a swine, a bovine, a drosophila, and a nematode. Claim 9 is directed to a biomarker comprising the polypeptide of claim 1. Claim 10 recites that the biomarker detects at least one selected from the group consisting of Notch signal transduction, cell differentiation, tumor, apoptosis, and Alzheimer's disease. Claims 7 and 20 recite that the amino acid sequence of the polypeptide is selected from the group consisting of SEQ ID NOS: 10-18 in which one or several of amino acids are deleted, substituted, or added.

(i) The specification of the instant application teaches that the polypeptide of the invention is produced and released as a result of the proteolysis (S4 cleavage) of a Notch protein that occurs simultaneously with either before or after the proteolysis of the Notch protein at a S3 cleavage site (page 5, lines 1-4). The specification discloses that proteolysis (S4 cleavage) occurs on a N-terminal side with respect to the S3 cleavage site in a transmembrane domain of the Notch protein (page 5, lines 4-6). At page 6, lines 17-19, the specification teaches that the amino terminus of NEXT is produced as a result of extracellular cleavage by TACE. The specification states that the NEXT resulting from the S2 cleavage then undergoes S3 cleavage, and the NICD resulting from the S3 cleavage translocates to the nucleus (page 6, lines 19-21). The specification indicates that cleavage at S4 occurs simultaneously with or either before or after the S3 cleavage, so that Nβ is released to an extracellular space (page 6, lines 21-25; Examples 2 and 3 at pages 11-12). Thus, the Notch-β or Nβ polypeptide of the claimed invention is derived from the proteolysis of NEXT derivatives. However, the specification does not teach any methods or working examples that indicate all possible fragments of a Notch protein (from any number of different species) comprise the claimed polypeptide. The specification and relevant literature

even indicate that there are four different Notch receptors (page 6, line 30;; Harper et al. Clin Genet 64: 461-472, 2003; page 461, column 1). Thus, undue experimentation would be required of the skilled artisan to generate a polypeptide comprising all possible Notch receptor fragments from many different species, a Site-2 cleavage site, and a Site-4 cleavage site. Such experimentation is considered undue. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The specification also does not teach all possible polypeptide variants of the amino acid sequences of SEQ ID NOs: 10-18, wherein one or several amino acids are deleted, substituted, or inserted. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994,

The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the Nβ polypeptide which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

(ii) The specification teaches that a biomarker according to the present invention contains the polypeptide and can be used for detecting Notch signal transduction, cell differentiation, tumor, apoptosis, and Alzheimer's disease (page 5, lines 29-32). The specification discloses that the Nβ polypeptide of the present invention is released to an extracellular space when NICD (Notch intracellular cytoplasmic domain) translocates to a nucleus as a result of the intramembranous endoproteolysis that occurs subsequent to the extracellular proteolysis (page 3, lines 1-5). NICD translocation to the nucleus regulates the transcription of target genes (page 2, lines 1-5). Examples 3-4, 6-8 of the instant specification (pages 11-13, 14-18) disclose that Nβ release to the extracellular space is caused by presenilin dependent proteolysis. However, the instant specification does not teach any methods or working examples that show a nexus between the claimed Nβ polypeptides and cell differentiation, tumor, apoptosis, or Alzheimer's disease. A large quantity of experimentation would be required by one skilled in the art to determine such. The limited guidance in the specification is not adequate and is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For instance, is an increase or decrease in the presence Nβ polypeptides correlated with cell differentiation, tumor, apoptosis, and Alzheimer's disease?

Due to the large quantity of experimentation necessary to generate a polypeptide comprising all possible Notch receptor fragments and derivatives of the amino acid sequence of SEQ ID NO: 13 and establish a nexus between the claimed Nβ polypeptides and cell differentiation, tumor, apoptosis, or Alzheimer's disease; the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to recite limitations of the Notch fragment, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

9. Claims 1-3, 7-11, 20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The basis for this rejection is set forth for claims 1-5 at pages 6-9 of the Office Action of 18 June 2008.

Claim 1 is directed to an isolated or synthesized polypeptide, wherein the polypeptide is a fragment of a Notch protein, N-terminal of the polypeptide is Site-2 cleavage site of the Notch protein that is positioned near a surface of cell membrane, C-terminal of the polypeptide is Site-4 cleavage site of the Notch protein that is positioned on N-terminal side in a transmembrane domain of the Notch protein relative to Site-3 cleavage site, wherein the Site-3 cleavage site is positioned at either inside the cell membrane or in close proximity to the cell membrane inside the cell, the polypeptide comprises at least a part of the transmembrane domain of the Notch

protein, the polypeptide is produced and released to an extracellular space as a result of proteolysis at the Site-4 cleavage site that occurs simultaneously with, before, or after proteolysis at the Site-3 cleavage site, wherein the proteolysis at the Site-3 cleavage site occurs subsequent to proteolysis at the Site-2 cleavage site and translocates Notch intracellular cytoplasmic domain (NICD) to a nucleus of the cell, and the Notch protein is a Notch protein that exists in an at least one organism selected from the group consisting of a human, a mouse, a rat, a rabbit, a goat, a swine, a bovine, a drosophila, and a nematode. Claims 7 and 20 recite that the amino acid sequence of the polypeptide is at least one selected from the group consisting of SEQ ID NOS: 10-18 in which one or several of amino acids are deleted, substituted, or added.

Applicant's arguments (20 October 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At page 10 of the Response, Applicant argues that the Notch protein is the same protein as that existing in a human, mouse, rat, rabbit, goat, swine, bovine, drosophila, or nematode. Applicant cites the relevant pages of the specification that show the polypeptide was isolated by various methods and was in possession of Applicants at the date of filing.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, as discussed in the previous Office Action of 18 June 2008, the claims of the instant application do not require that the Notch protein fragment or variants of the amino acid sequence of SEQ ID NO: 13 possesses any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of Notch protein fragments and variants of the amino acid sequence of SEQ ID NO: 13. One skilled in the art could not envision the detailed chemical structure of all or a significant number

of encompassed Notch protein fragments and variants of the amino acid sequence of SEQ ID NO: 13, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product itself is required. The broad brush discussion of making and isolating polypeptides does not constitute a disclosure of a representative number of members. The descriptions of one Notch protein fragment species (a NEXT fragment) and the Nβ amino acid sequence of SEQ ID NO: 13 are not adequate written description of an entire genus of functionally equivalent Notch protein fragments or variants of SEQ ID NO: 13.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

10. Claims 1-3, 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Mumm et al. (Mol Cell 5: 197-206, 2000). It is noted that claim 1 has been broadly interpreted by the Examiner as reading upon any polypeptide comprising a Notch fragment, Site-2 cleavage site,

and a Site-4 cleavage site. The basis for this rejection is set forth for claims 1-5 at page 9 of the previous Office Action of 18 June 2008.

Applicant's arguments (20 October 2008), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

At pages 10-11 of the Response, Applicant states that Mumm discloses the Site-2 cleavage and Site-3 cleavage, which are NEXT producing cleavage. Applicant asserts, though, that Mumm fails to disclose the Site-4 cleavage site of the Notch fragment, which may be C-terminal of the fragment of the Notch protein and may be positioned on a N-terminal side of the Notch protein relative to the Site-2 cleavage site.

Applicant's arguments have been fully considered but are not found to be persuasive.

Mumm et al. teach that activated Notch proteins and the full-length receptor responding to ligand binding are cleaved at a novel proteolytic site, termed S2, within the extracellular juxtamembrane region of Notch (abstract; page 202, column 2, first full paragraph; Figures 1, 2 and 6). The resultant carboxyl product is termed, NEXT (Notch extracellular truncation) (page 197, column 2, 2nd full paragraph). The NEXT protein isolated by Mumm et al. inherently contains a Site-4 cleavage site C-terminal to the Notch protein fragment (and positioned on a N-terminal side relative to the Site-3 cleavage site) (see Figure 7A, 7B of Mumm et al.). Although Mumm et al. does not discuss a Site-4 cleavage site, inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)). Applicant is also reminded

that the claims are directed to polypeptide product and not a method of producing such polypeptide.

11. Claims 1-3, 7-11, and 20 are rejected under 35 U.S.C. 102(a) and 35 U.S.C. 102(e) as being anticipated by Roberts et al. (WO 01/75435).

Roberts et al. teach an isolated S2-cleaved human Notch-1 amino acid sequence that is 94.1% identical to the amino acid sequence of SEQ ID NO: 10 of the instant application and 96.2% identical to the amino acid sequence of SEQ ID NO: 18 of the instant application (see SEQ ID NO: 11 of Roberts et al. and Figure 5; see also sequence alignment attached to the instant Office Action as Appendix A). The Notch-1 fragment of Roberts et al. is 41 amino acids in length and differs from the amino acid sequences of SEQ ID NOs: 10-18 at position 12. Although Roberts et al. does not indicate that human Notch-1 fragment comprises a Site-4 cleavage site, inherent anticipation does not require that one of ordinary skill in the art recognize an inherent feature in a prior art disclosure (*Schering Corp. v. Geneva Pharmaceuticals Inc.*, 67 USPQ2d 1664 (CAFC 2003); *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)). Furthermore, the Notch-1 fragment of Roberts et al. would be released to the extracellular space in proportion to Notch signal transduction, resulting from presenilin-dependent proteolysis, absent evidence to the contrary (*In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)).

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
17 April 2009

/Bridget E Bunner/
Primary Examiner, Art Unit 1647

Appendix A

```
AAE12904
ID   AAE12904 standard; protein; 41 AA.
XX
AC   AAE12904;
XX
DT   15-JAN-2002  (first entry)
XX
DE   Human Notch-1 protein fragment.
XX
KW   Alzheimer's disease; gamma-secretase; integral-membrane protein;
KW   beta-amyloid precursor protein; betaAPP; Notch-1 protein.
XX
OS   Homo sapiens.
XX
PN   WO200175435-A2.
XX
PD   11-OCT-2001.
XX
PF   30-MAR-2001; 2001WO-US010453.
XX
PR   03-APR-2000; 2000US-0194495P.
XX
PA   (BRIM ) BRISTOL-MYERS SQUIBB CO.
XX
PI   Roberts SB,  Hendrick JP,  Vinitsky A,  Lewis M,  Smith DW,  Pak R;
XX
DR   WPI; 2001-648575/74.
XX
PT   Novel gamma secretase protein, useful in the production of amyloids, is
PT   capable of cleaving beta-amyloid precursor protein to produce beta
PT   amyloid peptide.
XX
PS   Disclosure; Fig 5; 127pp; English.
XX
CC   The invention relates to the field of plaque amyloid deposits that are
CC   the hallmarks of Alzheimer's disease. In particular, the invention
CC   relates to an isolated, functionally-active protein that has gamma-
CC   secretase activity. Gamma-secretase activity is necessary for amyloid
CC   production. The present invention also relates to methods for isolating
CC   integral-membrane proteins and protein complexes, including the gamma-
CC   secretase protein of the invention. The method is useful for monitoring
CC   the cleavage of beta-amyloid precursor protein (betaAPP) by gamma-
CC   secretase. The present sequence is human Notch-1 protein fragment. This
CC   sequence is cleaved by gamma-secretase
XX
SQ   Sequence 41 AA;

  Query Match             96.7%;  Score 89;  DB 1;  Length 41;
  Best Local Similarity   94.1%;  Pred. No. 9.7e-05;
  Matches   16;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 VQSETVEPPPPSQLHFM 17
              ||||||||||:|||||
Db          1 VQSETVEPPPPAQLHFM 17
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Appendix B

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AAE12904
ID   AAE12904 standard; protein; 41 AA.
XX
AC   AAE12904;
XX
DT   15-JAN-2002  (first entry)
XX
DE   Human Notch-1 protein fragment.
XX
KW   Alzheimer's disease; gamma-secretase; integral-membrane protein;
KW   beta-amyloid precursor protein; betaAPP; Notch-1 protein.
XX
OS   Homo sapiens.
XX
PN   WO200175435-A2.
XX
PD   11-OCT-2001.
XX
PF   30-MAR-2001; 2001WO-US010453.
XX
PR   03-APR-2000; 2000US-0194495P.
XX
PA   (BRIM ) BRISTOL-MYERS SQUIBB CO.
XX
PI   Roberts SB,  Hendrick JP,  Vinitsky A,  Lewis M,  Smith DW,  Pak R;
XX
DR   WPI; 2001-648575/74.
XX
PT   Novel gamma secretase protein, useful in the production of amyloids, is
PT   capable of cleaving beta-amyloid precursor protein to produce beta
PT   amyloid peptide.
XX
PS   Disclosure; Fig 5; 127pp; English.
XX
CC   The invention relates to the field of plaque amyloid deposits that are
CC   the hallmarks of Alzheimer's disease. In particular, the invention
CC   relates to an isolated, functionally-active protein that has gamma-
CC   secretase activity. Gamma-secretase activity is necessary for amyloid
CC   production. The present invention also relates to methods for isolating
CC   integral-membrane proteins and protein complexes, including the gamma-
CC   secretase protein of the invention. The method is useful for monitoring
CC   the cleavage of beta-amyloid precursor protein (betaAPP) by gamma-
CC   secretase. The present sequence is human Notch-1 protein fragment. This
CC   sequence is cleaved by gamma-secretase
XX
SQ   Sequence 41 AA;

  Query Match             97.7%;  Score 130;  DB 1;  Length 41;
  Best Local Similarity   96.2%;  Pred. No. 1.8e-10;
  Matches   25;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 VQSETVEPPPPSQLHFMYVAAAAFVL 26
              ||||||||||:||||||||||||||
Db          1 VQSETVEPPPPAQLHFMYVAAAAFVL 26
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